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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/717,773	11/20/2003	Kurt Allen Josef	CEPH-2311	8378

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EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 02/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/717,773	JOSEF ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Pursuant

Pursuant to the directives of the preliminary amendment filed 11/20/03, claims 1-28 have been cancelled, and claims 29-51 added. Claims 29-51 are pending.

✧

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims encompass treatment of neurodegeneration, stroke, Alzheimer's Disease, amyotrophy, motor neuron damage, and acute CNS injury. The factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. [*Ex parte Forman* (230 USPQ 546, 1986)]. Applicants data is limited to a showing that a few of the claimed compounds an inhibit calpain I in a cell-free assay. The reality is that,

where protease inhibition is concerned, an attempt to extrapolate from such inhibition *in vitro* to therapy of one of the recited disorders is an exercise resulting in an "unpredictable" outcome. Consider the following:

- Chen, M. (*Frontiers in Bioscience* **3** A66-75, 1998) discusses the possible role of calpain in Alzheimer's Disease. As conveyed in the reference, there is evidence both for and against calpain acting as an *alpha*-secretase. (See, e.g., page 9, last paragraph). This reference neither "proves" nor disproves that one can "treat" Alzheimer's Disease with a calpain inhibitor. It does, however, raise considerable doubt as to whether calpain places a critical role in the progression of this disease. Given that there is uncertainty about whether calpain even plays a critical role in Alzheimer's Disease, it is fair to say that any therapeutic benefit of calpain inhibition is "unpredictable".

- Kavita (*J. Biol Chem* **270**, 27758-65, 1995) discloses (e.g., p. 27764) that P388D1 macrophage lysate contains a factor that protects precursor IL-1 *beta* protein from calpain proteolysis. This supports the proposition that if one has obtained data on inhibition of calpain in a cell-free system, one cannot necessarily predict the outcome of such inhibition if cellular constituents are present in an *in vitro* system. If extrapolation from a cell-free incubation mixture to a simple *in vitro* system is unpredictable, it stands to reason that extrapolation from a cell-free incubation mixture to physiological milieux would also be unpredictable.

- Harriman (*Journal of Pharmacology and Experimental Therapeutics* **294** (3) 1083-7, 2000) discloses (e.g., page 1087) that some compounds wth high potency to purified calpain were ineffective in reducing calpain activity in renal proximal tubules (RPT), and that this might be due to their limited uptake into RPT. Also stated (page 1087) is the following: "No clear correlation was obtained between the inhibitory constants of calpain and cytoprotection".

- Saez-Torres (*Clinical and Experimental Immunology* **121**, 151, 2000 discloses that peptide T inhibits T cell activation and cytokine production, but that it was not effective *in vivo* to treat EAE (experimental automimmune encephalomyelitis). This supports the assertion that where inflammation neurodegenerative disorders are concerned, one cannot predict therapeutic efficacy on the basis of an *in vitro* assay. As disclosed in Shields (*Proc Natl Acad Sci* 95, 5768, 1998), calpain is upregulated

and secreted by activated T cells. Thus, if compounds which are effective to inhibit activation of T cells are not effective to treat EAE, it stands to reason that one cannot "predict" the therapeutic efficacy of calpain inhibitors to treat EAE either. [See also the following references for evidence of a direct connection between calpain activity and activated T-cells: Schaecher, K (*Journal of Neuroimmunology* **129** (1-2) 1-9, 2002); Schaecher, K. E. (*Journal of Neuroimmunology* **119** (2) 333-42, 2001); Rock, M. T. (*Experimental Cell Research* **261** (1) 260-70, 2000)].

- Steinberg (*The Scientist* **16**, 22, 2002) discloses that when researchers vaccinated transgenic mice that had developed AD-like pathology, placques "melted away". In addition, favorable results were obtained in cognitive experiments with the mice. However, when attempted in humans, the Alzheimer's symptoms worsened. While the reference does not discuss calpain inhibition, the reference nevertheless supports an assertion of "unpredictability" in the treatment of AD. Applicants, for their part, have shown no evidence that any of the claimed compounds can be used to treat AD.

- Haas (*Journal of Leukocyte Biology* **63** (3) 395-404, 1998) discloses that calpain inhibitors were without effect in the inhibition of proinflammatory cytokine production. Haas supports the conclusion that if applicants' compounds were administered to an animal (or human) suffering from inflammation, proinflammatory cytokine production would continue unabated in spite of the presence of the compounds. Given that proinflammatory cytokine production will continue unabated, one cannot "predict" therapeutic efficacy in the treatment of inflammation using applicants' compounds. A similar conclusion arises from Rossi (*J Biol Chem* **273**, 16446, 1998) which discloses that the propensity of compounds to inhibit NF-*kappa* B cannot be predicted on the basis of their propensity to inhibit calpain.

In accordance with the foregoing, extrapolation from applicants' limited *in vitro* data to a therapy of any of the recited disorders is "unpredictable", and "undue experimentation"

would be required to practice the claimed invention.

✧

Claims 29-51 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claim 29 recites that n is 0 to "about" 6. This renders the claim indefinite as to the upper limit on integer variable "n".

- Claim 29 recites the following phrases:

  2 to about 14 carbons

  3 to about 10 carbons

  The presence of the qualifier "about" renders the claim indefinite as to the upper limit.

✹

References 1, 4 and 20 were stricken from the IDS because no copy of any of these was provided.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber, can be reached at 571-272-0925. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

DAVID LUKTON
PATENT EXAMINER
GROUP 1205